

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

NIKOLAI FRANZ GREGOR SCHWABE, et al.)

APPLN NO.: 10/769,831)

) GROUP ART UNIT: 1644

FILED: FEB. 2, 2004)

) EXAMINER:

CHIMERIC MHC PROTEIN AND
OLIGOMER THEREOF)

) DIBRINO, MARIANNE NMN

)

Customer No.: 02071

Confirmation No.: 2164

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

Sir:

RULE 1.132 DECLARATION OF GERALD T. NEPOM

I, Gerald T. Nepom, do hereby declare as follows:

1. I am the Director of the Benaroya Research Institute at Virginia Mason Medical Center in Seattle, Washington. A current copy of my *Curriculum Vitae* is attached hereto. For many years before and after the date of the present application I and the group I am heading have been recognized by others in the art as leaders in advancing Major Histocompatibility Complex (MHC) multimer technology.

2. I have carefully read the above United States patent application, the Examiner's office action mailed on January 4, 2007 (the "Office Action"), and all prior art references cited and relied upon in the Office Action.

3. I am familiar with the level of skill which would have been possessed by a person of ordinary skill in the art relevant to the above patent application as of the filing date of the application. Such a person at the time of the filing date of this patent application would have possessed a Masters or Ph.D. level of education and experience in the field of molecular biology, for example, and would have been sufficiently skilled, and aware of techniques, to produce MHC dimers or tetramers using a variety of scaffold components, e.g., IgG, leucine zippers and/or strepavidin. In the construction of MHC tetramers which are tetramerized through coupling to streptavidin the use of leucine zippers for

stabilization of each heterodimeric MHC monomer in the tetramer was well documented in the art and used routinely in my lab as of the filing date of the application. This is the use that is also described in US2005/003431A1.

4. In my opinion, notwithstanding the level of skill which would have been possessed by a person of ordinary skill in the art at the time the present application was filed, the subject matter claimed in Claim 1, and those claims depending therefrom, of the above-referenced patent application would not have been obvious to a person of ordinary skill in the art at the time of the filing of the present patent application. This is so because, at the time of the filing of this application, there was no reason for a person of ordinary skill in the art to consider combining the coiled-coil pentameric structure specified in Claim 1 with MHC complex. The closest reference, Terksikh, et al., recommended using small peptide structures, and at least by inference recommended against large macromolecular structures. In fact, it was noted at page 1668, lines 31-35, of the Terksikh, et al. reference that "... the display of short peptides in a pentameric form on Pab molecules bypasses the folding problems and the difficulties previously encountered during the expression of oligomeric forms of relatively complex proteins, such as single chain Fv fragments" When read in the context of the rest of Terksikh, et al. and with the knowledge and common sense of one of ordinary skill in the art at the time the present application was filed, this passage of Terksikh, et al. would have been viewed by one of ordinary skill in the art at the time this application was filed as discouraging the use of a coiled-coil protein like that of the present invention for MHC multimers. The MHC peptide structure specified by Claim 1 of the present application is even more complex than the single-chain Fv fragments referenced in the quoted portion of the reference, and the MHC peptide structure would have been understood to be a large macromolecular structure by those of ordinary skill in the art at the time of this invention.

5. For similar reasons, the IgM pentamer structures would not have suggested or made apparent the invention claimed in present Claim 1 and those claims depending therefrom. A person of ordinary skill in the art at the time of this invention would have understood that there is a big difference between an IgM pentamer scaffold and a coiled-coil protein (e.g., COMP), since the Ig variable domains are structurally similar in size and orientation to the MHC domains which are used in the multimers. Thus, while the

extension from the IgG dimers to IgM pentamers might possibly have been considered readily apparent to a person of ordinary skill in the art at the time of the filing date of this application, the change in scaffold to the coiled-coil protein would not.

6. Beyond the reasons stated above, there were a large number of biochemical and structural reasons why a person of ordinary skill in the art at the filing date of this application would not have found obvious the use of the coiled-coil proteins of the invention as a scaffold to multimerise MHC molecules, as in the claimed invention in Claim 1 and the claims depending therefrom. These include issues of protein solubility, stereochemistry, steric inhibition with function and folding, misfolding of the macromolecular ligand, and orientation of the assembled complex. There simply was no way, *a priori*, to predict that these significant issues would actually be able to accommodate the MHC peptide structure as ligand attached to a portion of the coiled-coil protein. Nor would there have been any motivation, from the cited literature or from the body of common knowledge, for a person of ordinary skill at the relevant time to attempt such a combination with any reasonable expectation of success. In general, multimeric molecular scaffolds of the immunoglobulin type are not assumed to be interchangeable with coiled-coil proteins such as the oligomerising domain of COMP.

7. I have further reviewed the language of Claim 4 in the patent application, and in particular the phrase "... is derived from ...". It is my opinion that a person of ordinary skill in the art at the time this patent application was filed would have been reasonably apprised of the subject matter being claimed with the use of this language, it having a reasonable degree of particularity and distinctness when the claim is read in light of the rest of the patent application specification. Such a person of ordinary skill in the art would know, within a reasonable level of certainty, whether the oligomerising domain in the second section is derived from the specified domain of COMP (and therefore within the scope of the claim) through well-known and common techniques, including for example, alignment of amino acid sequences, and this is made clear in the present patent application original Specification. See, e.g., paragraph 0050 thereof.

8. I further hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: July 4, 2007

Signed: / Gerald T Nepom /
Gerald T. Nepom, M.D., Ph.D.

Curriculum Vitae

GERALD THOMAS NEPOM

Date of Birth: November 15, 1950

Citizenship: USA

Married: to Barbara S. Nepom, M.D.

Education:

Harvard University, Cambridge, MA;
A.B., Biochemistry, magna cum laude, 1972

University of Washington School of Medicine, Seattle, WA;
Ph.D., Biochemistry, 1977;
M.D., 1978

Post Doctoral and Academic Appointments:

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| 1978-1979 | Flexible Medical Resident; Carney Hospital, Boston, Massachusetts |
| 1979-1980 | Research Fellow, Dept. of Pathology, Harvard University Medical School, Boston, Massachusetts |
| 1981 | Instructor, Dept. of Pathology, Harvard Medical School, Boston, Massachusetts |
| 1982-1985 | Assistant Member, Division of Immunology, Fred Hutchinson Cancer Research Center, Seattle, WA |
| 1984-1985 | Senior Scientist and Program Manager, HLA Laboratories, Genetic Systems Corporation, Seattle, WA |
| 1982-present | Affiliate Faculty, University of Washington School of Medicine, Seattle, WA <i>Dept. of Pathology:</i> Asst. Professor 1982-8, Assoc. Professor 1988-9; <i>Dept. of Immunology:</i> Assoc. Professor 1989-92; Professor, 1993-present. |
| 1985-present | Member and Scientific Director, Virginia Mason Research Center (<i>renamed Benaroya Research Institute in 2003</i>), Seattle, WA. Associate, Immunology and Rheumatology Sections, Virginia Mason Clinic; |
| 1993-present | Director, Benaroya Research Institute at Virginia Mason |

Editorial Boards & Review Committees:

| | |
|-----------|--|
| 1986-90 | Associate Editor, <i>The Journal of Immunology</i> |
| 1987-90 | Committee on Research Review, American Diabetes Assoc. |
| 1989-97 | Editorial Board, <i>Diabetes</i> |
| 1990-2002 | North American Editor, <i>Autoimmunity</i> |
| 1990-2006 | Editorial Board, <i>Tissue Antigens</i> |
| 1991-96 | Immunological Sciences Study Section, NIH (Chairman, 1994-96) |
| 1992-97 | Consulting Editor, <i>Journal of Clinical Investigation</i> |
| 1992-96 | Editorial Board, <i>Arthritis and Rheumatism</i> |
| 1993-- | Editorial Board, <i>Transgene</i> |
| 1997-- | Editorial Board, <i>Human Immunology</i> |
| 2000-2006 | Editorial Board, <i>J. Autoimmunity</i> |
| 2002-2006 | Faculty of 1000 |
| 2003 | Special Emphasis Panel (Chair), Innovative Grants on Immune Tolerance, NIAID, NIH |
| 2007-- | Chair, Juvenile Diabetes Research Foundation International, Medical Science Research Committee |

Service & Advisory Boards:

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|-----------|---|
| 1987-92 | Scientific Advisory Board, Cytel Corporation |
| 1996-99 | Scientific Advisory Board, Epoch Corporation |
| 1995-- | Scientific Advisory Board, Barbara Davis Center for Childhood Diabetes |
| 1996-01 | Scientific Advisory Board (Chair), Cedars-Sinai IBD Center |
| 1997-00 | Scientific Advisory Board, Cypress Biosciences |
| 1997-05 | Scientific Advisory Board, Xcyte Corporation |
| 2000-03 | Scientific Advisory Board, Diabetogen Biosciences |
| 2000-03 | Advisory Board, NARAC consortium, NIAMS |
| 2002-05 | Advisory Board, Abbott Scholars Program |
| 2002-05 | Advisory Board (Chair), Rheumatic Disease Center, UCSD |
| 2002 | Expert Panel (Chair), Autoimmune Diseases Coordinating Committee, National Institutes of Health |
| 2003-06 | Scientific Advisory Board, UCSF Diabetes Center |
| 2005-2008 | Finance Committee, American Association of Immunologists |
| 2005-- | Councilor, Clinical Immunology Society |

2001-2006 Scientific Advisory Board, Trubion Corporation
2005-2007 Vice-Chair and president-elect, Federation of Clinical Immunology Societies (FOCIS)
2007-- President, Federation of Clinical Immunology Societies (FOCIS)

Patents:

- Diagnostic probe for rheumatoid arthritis predisposition. U.S. Patent No. 4,971,902
- Allele-specific peptide epitope strategy for vaccine development. Australian Patent No. 1749597
- Diagnostic probe for diabetes Type I predisposition. U.S. Patent No. 5,039,606,
- Methods of MHC class II epitope mapping, detection of autoimmune T cells and antigens, and autoimmune treatment. U.S. Patent No. 7,094,555

Publications:

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Tamerius J, Nepom G, Hellstrom I and Hellstrom KE. Tumor-Associated Blocking Factors: Isolation from Sera of Tumor-Bearing Mice. *J. Immunol.* 116:724-730, 1976

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